

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference SCB746PCT		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/00078	International filing date (day/month/year) 07.01.2003	Priority date (day/month/year) 11.01.2002	
International Patent Classification (IPC) or both national classification and IPC A61L27/00, A61L27/00			
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Applicant FIDIA FARMACEUTICI S.P.A. et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 23.07.2003	Date of completion of this report 25.05.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heller, D Telephone No. +49 89 2399-8746 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/00078**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-8 as originally filed

Claims, Numbers

1-9 filed with telefax on 11.05.2004

Drawings, Sheets

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

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5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-9
Inventive step (IS)	Yes: Claims	
	No: Claims	1-9
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations

see separate sheet

SECTION V:

Prior art

Reference is made to the following documents:

D4 (EP-A- 0 341 745) concerns the use of the inner esters to manufacture sanitary and surgical articles, in the cosmetic and pharmaceutical fields, in the food industry and in many other industrial fields (p. 1, ll. 26 to 28).

D5 (WO99/61080) relates to the use of hyaluronic acid derivatives, with three-dimensional structures enclosing hollow spaces created by communicating pores and/or entangled fine, fibres or microfibrils, for the preparation of biocompatible biomaterials for in vivo regeneration of tissue cells (p. 1, ll. 6 to 13).

D6 (US 5 520 916) relates to a non-woven fabric material comprising hyaluronic acid derivatives, methods of production thereof, and methods of using said material in medical and pharmaceutical applications (col. 1, ll. 8 to 13).

D7 (WO00/01733) is directed to amides of hyaluronic acid and derivatives thereof for the preparation of pharmaceutical formulations, of biomaterials and for the coating of biomedical objects and the process for their preparation (p. 1, ll. 11 to 14).

D8 (WO00/54762) relates to methods for inhibiting angiogenesis in a mammal by the local administration of an activated hyaluronic acid composition to the site where the antiangiogenesis effect is desired. The anti-angiogenesis method of this invention can be used to control or inhibit solid tumor growth in cancer patients, to modulate wound healing, and to prevent or reduce inflammation (p. 1, ll. 5 to 9).

D9 (WO00/57896) provides peptides with a specific affinity for glycosaminoglycan molecules. These isolated peptides are formulated and administered by injection for the treatment or prevention of diseases involving cancer and angiogenesis (p. 3, ll. 21 to 32).

D10 (US 4 851 521) relates to polysaccharide esters and more precisely esters of hyaluronic acid and their use in the pharmaceutical and cosmetic fields, and in the field of biodegradable plastic materials (col. 1, ll. 6 to 12).

D11 (EP-A-0 466 300) relates to biocompatible viscoelastic polymeric gel slurries, methods for their preparation, formulations containing them, and medical uses thereof (p. 1, ll. 5 and 6).

D12 (Tonello et al.) discloses hyaluronan-based biomaterial for in vitro studies for angiogenesis (abstract; p. 1210, left col., last §).

D13 (Glass et al.) relates to a three-dimensional cell attachment matrix created by cross-linked hyaluronic acid (title).

D14 (Luo et al.) is directed to cross-linked hyaluronic acid hydrogel films as new biomaterial for drug delivery (title).

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D15 (Coradini et al.) discloses hyaluronic acid as drug delivery with improvement of the anti-proliferative activity on breast-cancer cell line.

Amendments

The amended claims do not fulfill the requirements of Articles 19 (2) and 34 (2) (b) PCT, in that they introduce new subject-matter which was not present in the application as originally filed.

Claim 1: The part "... wherein the carboxy groups ... or different hyaluronic acid molecule, ..." is neither supported by the description nor by the claims as originally filed. It is not allowed to refer to the content of a document cited only by reference in the description.

Claim 8: The term "and" is not supported by the description. "And" means that each combination of a form of the biomaterial is possible which is not the case with respect to the application as filed.

Claim 9: The terms "and care" seems to have no basis in the application as originally filed.

However, the present application has been treated under the assumption that the objections raised above have been overcome. Therefore, the following applies:

Subject-matter

Claim 1 is directed to the use of either

- a) benzyl ester of HA (hyaluronic acid) or
- b) a cross-linked derivative of HA derivative

for the preparation of a biomaterial suitable for angiogenic therapy to treat primary and secondary tumours.

Clarity

The term "for the preparation of a biomaterial" as used in claim 1 can be seen as "for the preparation of a medicament" and seems to be clear.

The term "cross-linked" as used in claim 1 does not fulfill the requirements of Article 6 PCT. It is unclear what is cross-linked.

The term "in association with" according to claims 2 and 6 is unclear. It is unclear how such an association looks like: as mixture, as complex, as combination ...

Novelty

The subject-matter of claims 1 to 16 is not new in the sense of Article 33 (2) PCT.

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The use of the biomaterial for the treatment of cancer as claimed in claims 1 to 9 is also already known from the following documents with their cited passages:
Even if D7 discloses the use of amides and is therefore not relevant concerning novelty vis-à-vis the benzyl ester of hyaluronic acid, hyaluronic acid esters are used to prepare amides which can be cross-linked (p. 4, ll. 14ff). Such a cross-linking falls within the scope of claim 1, the cross-linked derivatives of HA. Therefore, present claims 1 to 9 are not novel over D7 (see p. 1, ll. 11 - 14; claims 1, 5, 16, 21, 23).
The same applies for D8 (see claims 1-31) and D11 (see p. 3, ll. 35-47; p. 7, ll. 28-31). D10 (see col. 1, ll. 6-12; claims 1-8, 25) discloses the esters of HA even benzyl esters for the same treatment.

Inventive step

Even if the applicant is able to establish novelty it cannot be seen that any particular aspect of the application as filed would involve an inventive step under Article 33 (3) PCT in the light of the relevant prior art.

Priority

The applicant is informed that no check has been made as to whether priority has been validly claimed. Therefore, documents D1 to D3 (WO02/18448; WO02/41877; WO02/18450), which have been disregarded in writing the present opinion, could become relevant for the assessment of novelty once the present application enters the regional phase (Rule 64 (1) b PCT).

End. 4

CLAIMS

1. Use of benzyl ester of hyaluronic acid or a cross-linked derivative of hyaluronic acid wherein the carboxy groups of hyaluronic acid are cross-linked to the hydroxyl group of the same or different hyaluronic acid molecule, for the preparation of a biomaterial suitable for antiangiogenic therapy to treat primary and secondary tumours.
2. The use according to claim 1 wherein hyaluronic acid is in association with other natural, synthetic and/or semisynthetic biopolymers.
3. The use according to claim 2, wherein the natural biopolymer is selected from the group consisting of collagen, cellulose, polysaccharides, chitin, chitosan, pectins, agar, gellan and alginic acid.
4. The use according to claim 2, wherein the synthetic biopolymer is selected from the group consisting of polylactic acid (PLA), polyglycolic acid (PGA), polyurethanes and polysulphonic resins.
5. The use according to claim 2, wherein the semisynthetic biopolymer is selected from the group consisting of collagen cross-linked with aldehydes, diamine and gellan.
6. The use according to claim 1 wherein the biomaterial is associated with pharmacologically active substances.
7. The use according to claim 6, wherein the pharmacologically active substance is selected from the group consisting of fluorouracil, methotrexate, cis-platinum, carboplatin, oxaliplatin, ethopoxide, cyclophosphamide, vincristine, doxorubicin.
8. The use according to any one of claims 1-7 wherein the biomaterial is in the form of a non-woven felt, sponge, microsphere, film or membrane and/or other three-dimensional structures.
9. The use according to any one of claims 1-8, for the treatment and care of primary and secondary tumours when the tumour has been surgically removed and the cavity that is thus formed requires filling.

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